Transplantation of the Lung *

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TRANSPLANTATION of the lung presents special problems. First, it is an intrathoracic organ and one involved in respiration. Second, a degree of neuromuscular activity is essential to adequate respiratory function, without which life ceases abruptly. Third, immunologic rejection of the lung homograft is difficult to detect in its early stages and poor function of the transplant may be incorrectly attributed to organ ischemia during transplantation, to postoperative congestion perhaps secondary to lung denervation, or to the homograft reaction. Various of our series of lung transplants involving more than 400 animals were directed towards solving certain of these several problems.[1, 6-8]

Laboratory Studies

Lung Replantation. A particular advantage of lung autotransplantation or replantation is that it permits the development of technics and observations which are not influenced by the homograft reaction. The organ is merely removed from all attachments in the hemithorax, placed in a cold solution for variable periods of time, and then sutured in its original orthotopic position.

In a series of 68 mongrel dogs either the left or the right lung was reimplanted following pneumonectomy. The animals were anesthetized with pentobarbital sodium injected intravenously, and an endotracheal tube was inserted to permit rhythmical ventilation of the lung using a positive pressure apparatus. In the initial operations the bronchus, the pulmonary artery and the individual pulmonary veins were anastomosed. (Fig. 1) No attempt was made to restore continuity of the bronchial arteries. Unfortunately, a rather high incidence of postoperative thrombosis of the pulmonary veins was encountered. Thereafter a cuff of the atrium containing the inflowing pulmonary veins was excised with the lung, and the cuff was then used for an atrial anastomosis. This maneuver considerably decreased the incidence of thrombosis of the pulmonary veins and increased the number of chronic survivors. Silk sutures of suitable size were employed for each of the several anastomoses, the completion of which required approximately an hour. Each animal received penicillin and streptomycin daily for one week postoperatively.

The gross mortality rate approached 50 per cent, the major cause of death being thrombosis of the pulmonary veins postoperatively. However, in a certain number of dogs such complications as postoperative hemorrhage or diffuse pneumonia occurred. Few deaths occurred after the fourth week, and the chronically surviving dogs were studied in various ways which included chest auscultation, chest roentgenograms, and angiocardiograms. Bronchoscopy was performed periodically to determine the presence or absence of bronchial stenosis at the suture line, and this did occur in some

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animals. However, the majority of the animals did not develop strictures at the bronchial or vascular suture lines. Using differential bronchospirometry it was found that the function of the replanted lung declined abruptly to approximately one half the normal values over the first several days postoperatively, the oxygen uptake capacity being especially reduced. Thereafter the function of this lung gradually improved until by the 14th postoperative day low normal values were approached, but in almost no instance did a given lung regain the full functional capacity it had exhibited preoperatively.

Studies in Chronically Surviving Animals. Fifteen dogs which remained in good health and whose replanted lungs were well expanded were subjected to additional operative procedures several months following the first. Three dogs in which contralateral pneumonectomy was performed all resumed spontaneous respiration postoperatively. However, they displayed a pattern of slow, deep respiration with a long pause between expiration and inspiration, and with the participation of the accessory muscles of respiration. Thereafter the rate of respiration gradually slowed until they died in two, 24 and 18 hours postoperatively, respectively. Pulmonary edema was present in the first two dogs, but in the third dog respiration gradually deteriorated despite the absence of pulmonary edema, and at autopsy the anastomoses were found to be patent in all dogs. Thus it appeared that the replanted lung was not able to support the respiratory requirements of the animals after only approximately three months. Nevertheless, when other of these animals underwent contralateral pneumonectomy still later, it was found that some animals could survive removal of this opposite lung if the original replantation had been performed six months or more previously. This finding appeared to indicate either that parenchymal changes following replantation of the lung required six months to disappear, or that regeneration of the nerves to the replanted lung had occurred and now provided adequate reflex stimulation to respiration. The latter possibility is being studied further, since the usual postoperative parenchymal congestive changes could hardly be expected to persist for more than a few weeks—and in fact our differential bronchospirometry measurements have indicated that these changes persist for less than two weeks in most animals.

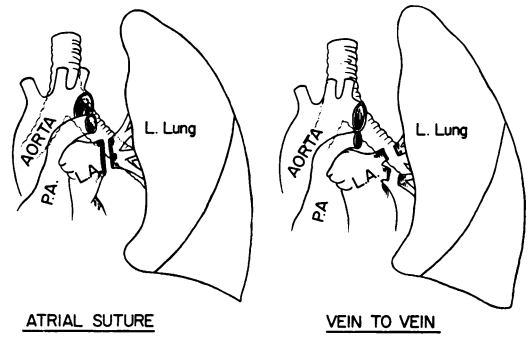

FIG. 1. Anastomoses in Lung Transplantation. The bronchial and pulmonary arterial anastomoses are routine. *Left.* In dogs, venous thrombosis is minimized by using for the anastomosis an atrial cuff into which the pulmonary veins drain. *Right.* In man, the pulmonary veins are of sufficient size to permit venous anastomoses with minimal risk of postoperative thrombosis.

In contrast to the inability of these animals to tolerate total contralateral pneumonectomy within less than six months following replantation, it was found that even several weeks following replantation of one lung the removal of several lobes of the opposite lung was tolerated in many dogs, with apparently normal respiratory rhythm being regained following recovery from the anesthetic. This was interpreted to indicate that the preservation of only a portion of the opposite lung maintained sufficient respiratory neural stimulus to employ effectively the respiratory capacity of the replanted lung; that it was only when the entire opposite lung was removed that the normal respiratory drive was not forth-

coming. This was also further emphasized by the fact that ligation of the opposite or contralateral pulmonary artery several weeks or months following replantation of the opposite lung was usually followed by normal respiratory rhythm but rapid rate, 50 to 70 per minute, which gradually slowed toward normal in a few days in those animals who survived the procedure. Of course, where even a small portion of the contralateral lung remained with normal ventilation and perfusion, it clearly provided a measure of respiratory support which rendered assessment of the reflex support from this lung more difficult to evaluate.

Lung Storage Followed by Replantation. A period of ischemia is unavoidable during lung transplantation, and thus a series of 46 dogs was studied to determine maximal limits of ischemia time that could be sustained with satisfactory lung function upon lung replantation. The usual procedure was to excise the lung and to store it in a cold solution at about 4° C. in the refrigerator. Although the lungs were periodically ventilated with oxygen through a sterile tube inserted into the bronchus in some animals, this ventilation was not done in the majority of experiments. It was found that the lung could be stored under these conditions for approximately two hours with the restoration of a gratifying degree of respiratory function following its replantation. Even four hours of storage were fairly well tolerated in some animals, but the level of function following replantation was not as good as that achieved at the end of only two hours of storage, and considerable pulmonary edema commonly developed. When the lung was stored for longer than four hours a bloody pulmonary edema frequently developed in this organ and caused death of the animal. However, in one animal storage for even 24 hours, followed by orthotopic replantation in the same animal, was tolerated with survival of both the animal and the lung.

From this series of experiments it was concluded that by cooling the lung following its excision one could expect almost routine restoration of a considerable degree of respiratory capacity in the replanted lung if it was stored at a low temperature for no more than two hours before blood flow was restored. This was to prove an important consideration in a subsequent clinical lung transplant.

Differential Division of Hilar Structures: Effects Upon Respiration. In view of the considerable amount of pulmonary edema and diminished pulmonary function which appeared to follow even immediate replantation of the lung, a series of studies was performed to determine the effects of the differential division of hilar structures upon the respiratory capacity of the lung. Bogardus [3] had reported that division of the bronchial arteries and the hilar adventitial arteries resulted in a strikingly decreased survival rate after contralateral pneumonectomy. The lung was found at autopsy to be heavy, wet hemorrhagic, and obviously incapable of supporting life. It was considered possible that in our own experiments, the division of the pulmonary lymphatics might have been a factor in producing the pulmonary edema that was observed.

Using a series of 23 mongrel dogs, five animals were operated upon and the lymphatics draining the left lung were divided along the main stem bronchus. Bronchospirometry and oxygen uptake measurements were performed on all animals before and immediately following operation, then three days later, eight days later and 12 days later. One dog died early following operation, but the other animals exhibited no marked effects from division of the lymphatics, except for the fact that pulmonary ventilation was somewhat reduced on the operated side. In a second group of five dogs the bronchial arteries were divided and bronchospirometric and oxygen

uptake measurements were again performed before and following operation and daily for six days thereafter. There was no significant change in the oxygen uptake by the operated lung, though there was a slight decrease in ventilation in three of the five animals. In a third group of five animals all tissue around the left bronchus and pulmonary vessels, including the bronchial artery, nerve supply and lymphatics, was divided. Lung function studies again revealed a significant decrease in both oxygen uptake and ventilation by the operated lung in three of these animals. It was considered possible that division of the vagus nerve was responsible for these changes which had not been present after division of the bronchial artery or the lymphatics in the other animals. It had of course been shown by others [12] that in certain species division of the vagus nerve will result in pulmonary edema.

In a fourth group of eight animals only the vagus nerve to the left lung was divided. In three of these the pulmonary artery pressure was measured before and after operation, and was followed for 48 hours by means of a catheter which was brought out through the skin. Bronchospirometric and oxygen uptake measurements were also performed. Two of these eight animals died early following operation. One exhibited pulmonary edema of the left or operated lung, and the other exhibited pulmonary edema of both lungs. In four of the remaining six animals there was a moderate decrease in ventilation and a substantial decrease in oxygen uptake by the left lung, but two animals showed little change. In the three animals in which measurements were taken, there was a gradual increase in pulmonary artery pressure. One of the animals showed a significant increase in pressure following operation and died postoperatively. At autopsy there was excessive edema in both lung fields, and this gross appearance was borne out by the microscopic studies. Although the pulmonary artery catheter was kept in place only a few days, it was concluded from such data as were available that the pulmonary artery pressure could be expected to rise moderately following either homotransplantation or replantation of a lung, but that the pressure gradually returned towards normal in dogs that survived, since dogs sacrificed months following the operation usually had a normal resting pulmonary artery pressure.

Comment. It should be noted at this point that disagreement continues regarding the effects of division of the various hilar structures upon the more subtle functions of respiration of the involved lung. This question requires much further study. It was our impression that division of the bronchial arteries had relatively little effect, but that division of the nerve supply to the lung did apparently have an effect in reducing the functional capacity of the lung.

Regeneration of Pulmonary Lymphatics Following Their Division. The reduction of lung function which almost invariably follows lung replantation or homotransplantation was thought possibly due to lymph stasis following division of the lung lymphatics. It had of course been shown by previous workers [4, 5] that lymph drainage from the lungs can represent a significant volume under some circumstances. Accordingly, studies were initiated to determine the rate of regeneration of the pulmonary lymphatics following their division.

The general procedure was to effect left lung replantation, and at various intervals of days thereafter to open this hemithorax and to inject Direct Sky Blue dye * into the replanted lung. At thoracotomy 24 hours following the first operation it could be seen that the dye spread to the level of the bronchial anastomosis but there stopped abruptly; none entered the lymphatic channels distal to the anastomosis and none

* Wyeth Laboratories, Philadelphia, Pa.

entered the hilar lymph nodes at 24 hours. A second dog underwent left lung reimplantation with re-exploration at 48 hours. Again, no dye crossed the anastomosis in this animal, nor did it do so in this animal at a third thoracotomy performed at 72 hours following the first operation. Nevertheless, by studying additional dogs in this general way it was eventually found that regeneration of the lymphatic channels could be detected approximately seven to twelve days following their division, and that by the end of from two to three weeks a large number of clearly visible lymphatic channels had been re-established across the bronchial anastomosis. It was of considerable interest that this regeneration of the lymphatics appeared to coincide with the reduction of congestion in the replanted lung and with the gradual improvement of the ventilatory and oxygen uptake capacity of the replanted lung.

Homotransplantation of the Lung in Dogs. Following the studies of replantation of the lung in which the effects of replantation and denervation had been evaluated, including those imposed by the unavoidable periods of ischemia involved in the replantation of the organ, a series of experiments was carried out in dogs in which lung homotransplantation was performed.[7] The operative technic employed in performing the lung homografts was identical to that used for lung replantation, except that the lung transplanted was derived from a second and genetically dissimilar animal. The left lung was used invariably in the 108 dogs so studied. The mean survival time of control animals was approximately 7.4 days. In contrast, the 20 of 34 animals treated with Imuran (azathioprine) * in a dosage of 4.0 mg. per Kg. per day by mouth survived the immediate postoperative period and lived an average of 30.4 days. Two of the 20 chronic survivors were permanent survivors, but at sacrifice many months later it was found that the homografted lung had been rejected at some time in the past and was encased in a fibrous envelope. The angiocardiogram in one of these two *permanent* survivors had been remarkably normal on the day prior to sacrifice, and this again emphasized that only by differential lung function studies, by sacrifice of the animal, or by ligation of the contralateral pulmonary artery could one be certain of the functional state of the homografted lung.

Homotransplantation of the lung was performed in additional groups of animals using other drugs (16 dogs with Imuran and hydrocortisone therapy, 20 dogs with Imuran and Actinomycin C, and 20 dogs with Methotrexate therapy). However, in our hands Imuran proved to be the agent which provided the greatest length of life in the greatest percentage of animals, though Blumenstock and co-workers [2] achieved gratifying results with Methotrexate. Certainly familiarity with the problems involved in the usage of a given drug can lead to better results with that drug.

The general conclusions derived from these studies were that, whereas control animals who survived the immediate postoperative period lived only an average of 7.4 days before rejection of the lung caused death, the animals who received effective suppressive drug therapy of virtually any type usually lived longer than the control animals. It was clear from these studies that homotransplantation of the lung in dogs could be performed with prolonged survival of the animals if meticulous attention were given to their postoperative care.

Lung Homotransplantation in Man

Once it was believed the operative technics and the postoperative problems involved in lung homotransplantation and suppressive therapy had been elucidated through studies involving a large number

* Burroughs Wellcome, Tuckahoe, N. Y.

of dogs, suitable patients were screened as possible candidates for lung homotransplantation. Actually, many months were to pass before a person was admitted to the hospital who appeared to fill the necessary criteria. First, it was believed that the initial patient with pulmonary insufficiency should have some additional disease which was likely to prove fatal in the foreseeable future, should transplantation of the lung result in an unanticipated complication which terminated fatally. Such a disease condition might be an extensive malignant tumor, but one without distant metastases. Second, the patient must have virtual destruction of one lung, preferably the left lung for technical reasons, so that the excision of this lung would not remove functioning lung tissue of the patient's own genetic composition. Third, the patient must have severe respiratory embarrassment, so that the function of the homotransplanted lung could conceivably render his remaining days more tolerable. Fourth, the patient must understand that the procedure was experimental, and he must be prepared to sign the necessary permission which would be properly witnessed by disinterested observers.

On April 15, 1963, a 58-year-old white man was admitted to the University Hospital with the diagnosis of repeated attacks of pneumonia. Careful studies demonstrated that he had a squamous cell carcinoma virtually occluding the left main stem bronchus with chronic purulent infection in this essentially destroyed lung. In addition, he had a chronic renal lesion bilaterally which had resulted in borderline renal insufficiency. He was losing massive quantities of protein in the urine, and his total serum protein level was 5.3 Gm./100 cc. with 0.5 Gm. of albumin and 4.8 Gm. of globulin. This extremely low albumin level was repeatedly confirmed with electrophoretic measurements. As has been recorded elsewhere,[8] after exhaustive studies it was concluded that this patient did fulfill the previously stipulated criteria, and he was willing to accept the lung homotransplant at the time the left lung was removed for the neoplastic obstruction with distal lung abscesses. He was somewhat dyspneic even at bed rest, and his exercise tolerance was severely limited.

The left lung homograft that was inserted had been obtained from a patient who had arrived in the emergency room an hour earlier with a massive myocardial infarction and pulmonary edema, who died despite all measures which the medical service could advance. The donor's cardiopulmonary activity had been maintained by closed chest cardiac massage and pulmonary ventilation with pure oxygen as he was transported to the operating suite and sterile thoracotomy and left pneumonectomy performed. A massive dose of heparin had been injected into the heart at the time of death. Following its excision the donor lung was preserved by tying a sterile tube into the bronchus and ventilating the organ rhythmically until all vascular anastomoses had been performed in the recipient, following removal of the recipient's left lung. In addition, the temperature of the lung was quickly reduced by the injection of cold glucose solution containing penicillin and heparin through the pulmonary artery. This had been continued with the lung partially submerged in a cold solution until the time came to insert it into the left hemithorax of the recipient. In this instance, venous anastomoses were employed rather than the atrial cuff, since the infection in the left hemithorax of the recipient rendered opening the pericardium of the recipient inadvisable. First the inferior pulmonary vein was anastomosed, then the superior pulmonary vein, next the pulmonary artery and finally the bronchus. As soon as the vascular anastomoses had been completed, additional heparin was injected through the pulmonary artery but the

clamps were not removed from the vessels, in that the anesthesiologist had found it possible to maintain the patient's respiration with the right lung; it was considered wise not to impose a functional shunt by releasing the clamps on the vessels in the left lung until the left bronchus had been anastomosed to make possible ventilation of this lung.

Immediately after all clamps had been removed from the bronchus and the vessels to the transplanted lung, the arterial oxygen saturation in the aorta was 98.7 per cent, whereas on several occasions preoperatively the arterial oxygen saturation in peripheral arterial blood had been approximately 87 per cent. Thus, the destroyed left lung had been participating very little in the respiratory support of the patient preoperatively, though it was still being perfused with blood. Postoperatively perfusion of the transplanted lung was demonstrated by angiocardiogram, and its effective participation as an organ of respiration was evidenced by the fact that the peripheral arterial oxygen saturation remained at almost 98 per cent for the approximately three weeks that the patient lived. This lung was never collapsed, and at autopsy there was virtually no evidence of immunologic rejection.

Postoperatively, the patient was given Imuran therapy in a dosage of approximately 4 mg./Kg./day, and a tracheostomy with a cuffed tube was employed to effect positive pressure ventilation intermittently. He reacted from the anesthetic promptly, and no particular problems referable to his lungs were experienced throughout the period that he lived. Nevertheless, his course was one that was gradually downhill. He had had a very poor appetite for weeks or even months prior to the operation, and his appetite did not improve postoperatively. It had been found at operation that there was extensive invasion in the region of the aorta and esophagus, and these deposits of tumor could not be excised, though preoperatively every effort had been made to exclude distant metastases by roentgenograms, scalene fat pad biopsy and pleural biopsy. The borderline renal insufficiency that was present preoperatively gradually became more severe, and despite large amounts of commercial albumin therapy it was not possible materially to increase his serum albumin level. The general debility and an azotemia increased slowly and he died on the 18th postoperative day.

At autopsy a most careful evaluation was made of the lungs and of the possible effects upon other organs. The gross appearance of the homotransplanted lung could not be distinguished from that of the patient's own lung, with the exception that once the vessels and bronchus were opened the anastomotic sites could be visualized. There was evidence that a small leak had occurred in the membranous portion of the bronchus of the transplanted lung, which one operator believed he had produced at bronchoscopy two days earlier when the patient had become unable to remove his own secretions. However, this small defect was walled off by adherent surrounding tissue and had caused no special problem. Angiograms and bronchograms were performed upon the homotransplanted lung, and both bronchi and pulmonary vessels were patent. Histologic studies revealed little or no evidence of immunologic rejection of this lung. Although the effectiveness of the azathioprine therapy may have been enhanced by the moderately severe azotemia which slowly developed postoperatively, the blood urea nitrogen level never reached 200 mg. per cent.

Discussion

A number of excellent studies of both lung replantation and homotransplantation have been reported. The initial lung replantation was apparently that of Juvenelle.[9] Blumenstock and his associates,[2] using

Methotrexate to suppress the immunologic response, achieved survival of the host and the homograft for more than six months in a few dogs.

In careful studies of lung replantation, Yeh, Ellison and Ellison [14] found that pulmonary ventilation was unaltered postoperatively but that blood oxygenation was significantly impaired. These findings were similar to our own and to those of Reemtsma and his co-workers.[13] Thus most investigators have found the ventilatory capacity of the replanted lung less markedly impaired than its capacity to transfer oxygen to the blood passing through it. Fortunately, these changes, which are maximal in the first days following operation, gradually recede to permit function of the replanted lung to improve substantially, though rarely to the preoperative level. Nigro and his group [11] studied five dogs which survived long periods after lung replantation followed later by contralateral pneumonectomy. They found the pulmonary artery pressures consistently elevated in these animals and considered this indicative of a pulmonary hypertensive state. Magovern and Yates [10] have recently reported a lung homotransplantation in man.

Future of Clinical Lung Transplantation. The future of lung transplantation in man is related to the problem of homograft tolerance in general. Through extensive animal studies in many laboratories it has been established that lung transplantation is technically feasible and that the transplant supplies a considerable degree of respiratory activity until rejected, in the case of an homotransplant. Furthermore, not only acute and chronic respiratory insufficiency but also cor pulmonale could be improved by lung homotransplantation if immunologic rejection could but be prevented. Thus the widespread clinical application of lung homotransplantation must await improved means of suppressing the homograft reaction. Meanwhile, further animal experimentation will supply additional answers to such questions as the optimal drug suppressive therapy available, the normal neural mediation of respiratory reflex activity and the importance of bronchial artery flow to complete functional integrity of the bronchial mucosa and the lung parenchyma, among others.

Summary and Conclusions

1. The technical and physiological problems of lung transplantation have been explored in more than 400 dogs.

2. Lung replantation provides a method for studying the effects of lung transplantation apart from those introduced by the homograft response. It was found by differential bronchospirometry that the respiratory capacity of the replanted lung was reduced to approximately one half the normal value for almost two weeks following operation. Thereafter the function of this lung gradually improved but rarely regained the preoperative level.

3. Storage of the lung at 4° C. for two hours, with replantation, was followed by lung survival and reasonably good respiratory capacity of this organ in most animals. However, storage of the lung for longer periods resulted in an increasing evidence of pulmonary edema upon replantation, and death of the animals was common following lung storage for more than four hours with replantation.

4. Bronchial lymph channels were found to begin regeneration within three or four days and to regenerate almost completely by the end of two weeks.

5. Homotransplantation of the lung was performed in a large number of dogs. The untreated control animals that survived the immediate postoperative period lived an average of seven days. Those dogs treated with azathioprine (Imuran) lived an average of 30 days.

6. The clinical experience with lung homotransplantation in man has been reviewed.

References

1. Alican, F. and J. D. Hardy: Lung Reimplantation; Effect on Respiratory Pattern and Function. J.A.M.A., **183**:849, 1963.
2. Blumenstock, D. A., J. A. Collins, E. D. Thomas and J. W. Ferrebee: Homotransplantation of the Lungs in Dogs Treated with Methotrexate. Surg. Forum, **12**:121, 1961.
3. Bogardus, G. M.: An Evaluation in Dogs of the Relationship of Pulmonary, Bronchial, and Hilar Adventitial Circulation to the Problem of Lung Transplantation. Surgery, **43**:849, 1958.
4. Courtice, F. C.: Lymph Flow in the Lungs. Brit. M. Bull., **19**:76, 1963.
5. Drinker, C. K.: The Lymphatic System. Ann. Rev. Physiol., **7**:389, 1945.
6. Hardy, J. D., S. Eraslan and M. L. Dalton, Jr.: Autotransplantation and Homotransplantation of the Lung: Further Studies. J. Thor. Cardiov. Surg., **46**:606, 1963.
7. Hardy, J. D., S. Eraslan, M. L. Dalton, Jr., F. Alican and M. D. Turner: Reimplantation and Homotransplantation of the Lung; Laboratory Studies and Clinical Potential. Ann. Surg., **157**:707, 1963.
8. Hardy, J. D., W. R. Webb, M. L. Dalton, Jr. and G. R. Walker, Jr.: Lung Homotransplantation in Man: Report of the Initial Case. J.A.M.A., **186**:1065, 1963.
9. Juvenelle, A. A., C. Citret, C. E. Wiles, Jr. and J. D. Stewart: Pneumonectomy with Replantation of the Lung in the Dog for Physiologic Study. J. Thor. Cardiov. Surg., **21**:111, 1951.
10. Magovern, G. J. and A. J. Yates: Human Homotransplantation of Left Lung. Ann. N. Y. Acad. Sci., (In Press).
11. Nigro, S. L., R. H. Evans, J. R. Benfield, O. Gago, W. A. Fry and W. E. Adams: Physiologic Alterations of Cardiopulmonary Function in Dogs Living One and One-Half Years on Only a Reimplanted Right Lung. J. Thor. Cardiov. Surg., **46**:598, 1963.
12. Rech, R. H., and H. L. Borison: Vagotomy-induced Pulmonary Edema in the Guinea Pig. Am. J. Physiol., **202**:499, 1962.
13. Reemtsma, K., R. E. Rogers, J. F. Lucas, F. E. Schmidt and F. H. Davis, Jr.: Studies of Pulmonary Function in Transplantation of the Canine Lung. J. Thor. Cardiov. Surg., **46**:589, 1963.
14. Yeh, T. J., L. T. Ellison and R. G. Ellison: Functional Evaluation of the Autotransplanted Lung in the Dog. Am. Rev. Resp. Dis., **86**:791, 1962.